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EDITORIAL

Update on sepsis and septic shock: from bundles to precision medicine

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From bundles to biology: why could protocolization in sepsis have reached a plateau

Sepsis and septic shock remain among the most critical clinical emergencies in acute care. For more than 2 decades, clinical progress has been built on standardization: early recognition, rapid administration of antibiotics, aggressive fluid resuscitation, and vasopressor support. Bundles have transformed sepsis care and unquestionably saved lives. However, in many well-resourced healthcare systems, mortality reductions have plateaued, and several recent trials have failed to demonstrate additional benefit when bundles are applied broadly to biologically heterogeneous populations. This ceiling effect reflects a fundamental limitation: sepsis is not a single disease but a spectrum of host responses, whereas protocolized care assumes relative biological uniformity. Importantly, sepsis outcomes remain highly variable across regions and institutions, and bundles continue to provide substantial benefit in low- and middle-income or resource-limited settings. Precision, biologically informed approaches should therefore be considered complementary and context-dependent, rather than a universal replacement for bundles.

Modern evidence demonstrates that a uniform therapy applied to a biologically heterogeneous syndrome is no longer sufficient. The paradigm is adapting protocolized intervention to precision medicine in sepsis, where treatment adapts to the patient's evolving biological endotype and trajectories. This transformation begins even before patients reach the ICU. More than 90% of sepsis develops in the community. Rudd et al. argue that sepsis must be approached not only as a critical care emergency but as a public-health priority. They propose a four-pillar model: mitigation, monitoring, measurement, and management, to intervene before organ dysfunction develops [1]. This framework reframes vaccination as sepsis prevention, advocates for risk-based post-discharge surveillance, and recognizes hospital-at-home pathways as a legitimate setting in which early treatment could be established. The critical question therefore becomes not how quickly sepsis care can be initiated once organ dysfunction is recognized, but how early the trajectory can be altered before organ dysfunction appears. Even the fastest bundle cannot reverse irreversible biology.

Sepsis as multiple syndromes: immune, endothelial, and metabolic endotypes

Biological heterogeneity in sepsis is now irrefutable. Sepsis is not defined solely by infection plus organ dysfunction. It represents diverging immune, endothelial, and metabolic responses. These responses evolve dynamically and interact in ways that reshape disease severity and response to therapy.

Temperature-trajectory phenotypes, for example, reveal distinct patterns of systemic inflammation and mortality: hypothermic patients show profound immunosuppression, whereas hyperthermic slow resolvers demonstrate sustained inflammation [2]. Metabolic studies identify subphenotypes driven by lysophospholipid signatures associated with endothelial activation and adverse outcomes. Patients who remain in low-lysophospholipid states experience persistent endothelial injury [3]. Companion transcriptomic analysis reveals that biological endotypes do not respond uniformly to immunomodulation, and some endotypes benefit from corticosteroids, while others appear harmed [4]. Baillie et al. extend this concept, proposing that meaningful

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endotypes should not be defined by clustering algorithms alone but anchored to modifiable mechanisms, so that therapies can be targeted rationally rather than empirically [5].

Immune paralysis illustrates how trajectory rather than a single value determines risk. Monneret and colleagues followed 1,023 septic shock patients and demonstrated that early low monocyte HLA-DR did not independently predict outcome; instead, failure to recover mHLA-DR by days 3–5 identified persistent immune dysfunction and increased mortality [6]. Sepsis-induced immunosuppression is therefore not a static label but a dynamic, measurable state that creates a window in which immunostimulatory therapies such as GM-CSF or IL-7 may be appropriate. Precision starts by identifying treatable biology.

The endothelial response forms the second axis of sepsis. A landmark review reframed sepsis as simultaneous failure of three interconnected systems: the immune system, the endothelium, and coagulation, rather than a linear cascade [7]. This triad model unifies previously competing theories and shifts therapeutic ambition away from escalating fluids and vasopressors and toward therapies that stabilize endothelial barrier integrity. At the same time, bedside tools are emerging. Optical coherence tomography angiography (OCTA) demonstrates real-time visualization of retinal microcirculation, offering a non-invasive window into tissue perfusion [8]. In a large multicenter study, echocardiography altered management in half of shock patients, yet fewer than half received an echocardiogram within 24 h.[9] Technology now allows clinicians to monitor the microcirculation, yet system inertia prevents its use.

Precision treatment: perfusion targets and stewardship

Sepsis protocols have saved lives by standardizing early recognition and treatment. Building on that foundation, current sepsis research is now inquiring into how biological markers may refine decisions in specific patients. Balanced crystalloids lower chloride and improve acid–base status, yet serum chloride or pH do not identify which patients benefit [10]. Targeting a higher MAP (80–85 mmHg) does not improve survival at the population level and may increase harm when vasopressor doses escalate despite evidence of peripheral hypoperfusion such as mottling [11]. However, this absence of average benefit does not exclude the possibility that selected patient subphenotypes may benefit from higher perfusion pressures, reinforcing the need for individualized resuscitation guided by physiological and biological context rather than fixed numerical targets [12]. Left-ventricular diastolic dysfunction, observed in nearly half of septic shock patients, was not associated with mortality and frequently resolved spontaneously [13]. These findings undermine the assumption that more fluids, more vasopressors, or tighter numbers are inherently beneficial. Instead, the goal of resuscitation must be restoring perfusion, not achieving arbitrary numerical thresholds.

Even the most definitive component of sepsis therapy, source control, is inconsistently defined. A scoping review across 77 studies revealed major variability in the definition, timing, and assessment of adequacy of source control, even though roughly two-thirds of studies demonstrated benefit [14]. Evidence is not the barrier; implementation is.

The past two years have also transformed antibiotic stewardship. The BLING III trial showed a trend toward improved clinical cure at day 14 with continuous β-lactam infusion, with effect estimates consistently favoring continuous infusion across prespecified subgroups [15]. These findings, together with established pharmacokinetic–pharmacodynamic principles, support the concept that patients at high risk of antibiotic underexposure (e.g., high cardiac output, augmented renal clearance, obesity, or extracorporeal support) may represent a biologically plausible target population for precision dosing strategies. The ADAPT-Sepsis trial showed that biomarker-guided discontinuation safely reduces duration of antimicrobial therapy [16]. The BALANCE trial established that 7 days of antibiotics is noninferior to 14 for bloodstream infection, including in ICU patients [17]. Shorter therapy is not under-treatment. It is precision.

Future directions: linking biology to decisions at the bedside

Meyer and Prescott synthesize the emerging paradigm: sepsis is not simply infection with organ dysfunction, but a dynamic convergence of immune, endothelial, and coagulation failure [18]. The next phase of progress lies not in discovering entirely new treatments but in applying existing ones to the right patient at the right time, guided by biology (Fig. 1). Clinical trials are transitioning from broad, unselected enrollment to more biologically stratified recruitment. Instead, future studies will recruit patients based on endotype. As an example, patients with sustained immunosuppression defined by monocyte HLA-DR or patients with endothelial injury reflected by elevated Ang-2 or lysophospholipid patterns. Similarly, monitoring will transition from single values to trajectory-based assessment, capturing how immune and endothelial states evolve over time. Resuscitation will no longer be driven by a single mean arterial pressure target but by adequacy of microcirculatory perfusion, informed by technologies such as OCTA or

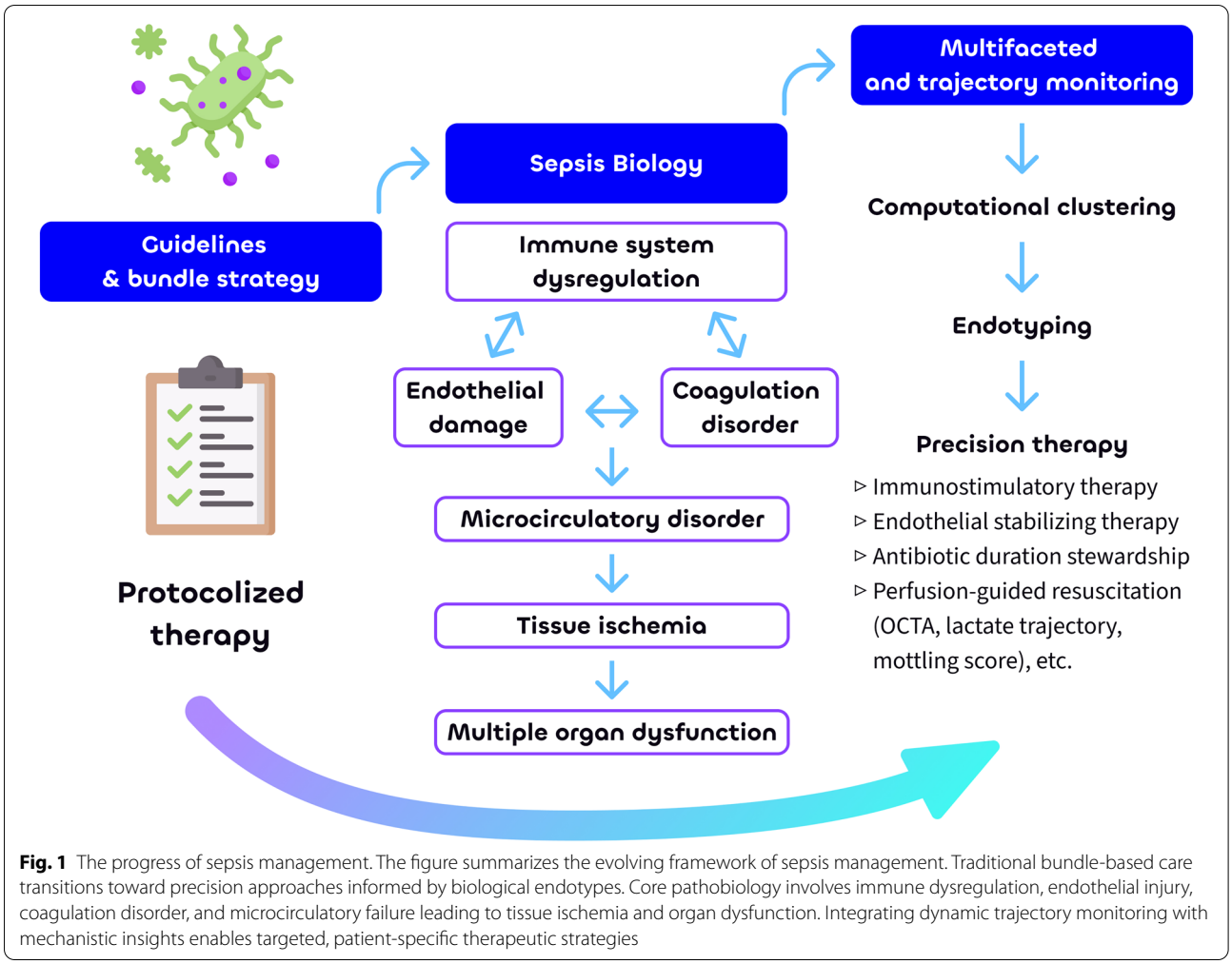

Fig. 1 The progress of sepsis management. The figure summarizes the evolving framework of sepsis management. Traditional bundle-based care transitions toward precision approaches informed by biological endotypes. Core pathobiology involves immune dysregulation, endothelial injury, coagulation disorder, and microcirculatory failure leading to tissue ischemia and organ dysfunction. Integrating dynamic trajectory monitoring with mechanistic insights enables targeted, patient-specific therapeutic strategies

early echocardiography. Antibiotic therapy, historically guided by fixed durations, will increasingly be determined by clinical and biological recovery.

Therefore, the principal consideration for clinicians and researchers has shifted from asking, "Does this therapy work in sepsis?" to determining, "Which specific therapy is most appropriate for each patient at a given time, informed by relevant biological markers?" The development of therapeutic bundles marked an initial step, while a deeper understanding of underlying biology represents the ultimate goal.

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